

Insulin-like growth factor system in remission and flare of inflammatory bowel diseases

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KEY WORDS

Crohn disease, inflammation, insulin-like growth factor 1, insulin-like growth factor-binding protein 3, ulcerative colitis

ABSTRACT

INTRODUCTION Insulin-like growth factor 1 (IGF-1) is involved in the modulation of immunity and inflammation. It also plays a role in regulating the migration of endothelial cells and production of vasoactive agents.

OBJECTIVES This study assessed the concentrations of IGF-1 and insulin-like growth factor-binding protein 3 (IGFBP-3) and their relationships to disease activity in patients with inflammatory bowel disease (IBD).

PATIENTS AND METHODS A total of 129 adult patients with IBD (69 with Crohn disease [CD] and 60 with ulcerative colitis [UC]) were involved in the study. The control group consisted of 31 healthy volunteers. Biochemical serum analyses were performed and the associations of IGF-1 and IGFBP-3 with inflammatory markers and disease activity were assessed.

RESULTS IGF-1 levels were decreased in patients with active UC compared with those with nonactive UC (mean [SD], 78.3 [22.7] ng/ml and 96.2 [24.5] ng/ml, respectively; $P = 0.02$) and controls (94.5 [26.5] ng/ml; $P = 0.03$). The IGF-1 level was lower in patients with active CD compared with those with nonactive CD (mean [SD], 79.2 [24.9] ng/ml and 110.1 [43.4] ng/ml, respectively; $P < 0.001$). The IGFBP-3 level was lower in patients with active UC compared with those with nonactive UC ($P = 0.04$) and controls ($P = 0.04$). IGF-1 correlated negatively with C-reactive protein (CRP) levels ($P < 0.01$), disease activity ($P < 0.05$), and disease duration ($P < 0.05$). IGFBP-3 levels correlated negatively with CRP levels ($P < 0.05$).

CONCLUSIONS The IGF system is disrupted in patients with IBD. Systemic levels of the IGF axis components are related to disease activity and duration.

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INTRODUCTION Inflammatory bowel diseases (IBDs), including Crohn disease (CD) and ulcerative colitis (UC), constitute chronic conditions, the etiology of which is not fully understood.

Patients with IBD are genetically predisposed to pathological interactions among intestinal microflora, some food components, and the immune system.¹ Changes in the balance between regulatory and inflammatory cytokines as well as endothelial dysfunction help maintain the inflammatory process.¹ Endothelial cells form the padding of the interiors of blood vessels and provide a protective barrier that regulates the flow of biomolecules and cells (eg, white blood cells) between

the blood and tissues.^{2,3} The cells are characterized by a highly active metabolism; they produce elements of the basement membrane, intercellular junctions, and numerous substances that regulate blood vessel tone and blood flow.^{1,3} In addition, the endothelium plays a key role in the normal functioning of the coagulation system and fibrinolysis through protein synthesis and interactions with blood platelets, and regulates the inflammatory response by acting on inflammatory cells.^{1,2,4} Activation of the endothelium triggers an increase in leukocyte adhesion, endothelial cell permeability to inflammatory cells, tone of the smooth muscular coat, and activity of the coagulation system.

One of the anti-inflammatory agents responsible for proliferation of endothelial cells and angiogenesis is insulin-like growth factor 1 (IGF-1), and its receptor is expressed in endothelial cells of small and large vessels.^{1,2,4}

IGF-1 is a 7.5-kDa peptide hormone produced primarily by mesenchymal cells in the liver.^{5,6} Its production is regulated by growth hormone (GH) secreted by the pituitary gland.^{5,7} In serum, IGF-1 binds to a family of insulin-like growth factor binding proteins (IGFBPs 1–6) that transport it to destination tissues.⁵ IGFBP-3 is the most abundant of the group of IGFBPs that transports and, particularly, controls the bioavailability and half-life of IGF-1.⁶ IGF-1 receptors are located in many cell types, mainly in the brain, skeletal muscle, smooth muscle, cartilage, and bone.^{2,8,9} The serum IGF-1 concentration depends on the GH level, insulin level, nutritional status, and physical activity.^{7,10} IGF-1 promotes growth and differentiation in a variety of tissues, maintains structural integrity, and inhibits apoptosis.⁷ It is also involved in modulating immunity and inflammation.¹¹ In addition, IGF-1 plays a major role in the function of endothelial cells² by regulating their migration and producing vasoactive agents (eg, nitric oxide), and the correct level of IGF-1 contributes to protection from atherosclerosis and cardiovascular diseases.^{2,6,7}

Decreased serum concentrations of IGF-1 and IGFBP-3 occur in patients with type 2 diabetes mellitus and increase the risk of complications and mortality.^{12,13} Dysregulation of the IGF system affects angiogenesis and may contribute to malignancies.² For example, systemic inflammation that can be found in rheumatoid arthritis results in resistance to GH and low circulating IGF-1 levels.^{14–17} Baker et al¹⁸ reported that the IGF-1 level becomes progressively lower in patients with more severe and long-standing rheumatoid arthritis. Tumor necrosis factor α (TNF- α) inhibits IGF-1 during the chronic inflammation process.¹⁹ In addition, Briot et al²⁰ showed that IGF-1 level increases in patients with ankylosing spondylitis who are treated with infliximab.

Our study investigated the associations between IGF-1 and IGFBP-3 concentrations and clinical activity of UC and CD, as well as disease duration.

PATIENTS AND METHODS **Recruitment of patients** Patients were recruited between October 2016 and December 2016. The study included a total of 129 consecutive adult patients diagnosed with IBD at the outpatient Department of Gastroenterology and Hepatology, University Hospital in Krakow, Poland. Sixty-nine patients were diagnosed with CD, including 36 men (52.2%) and 33 women (47.8%); the median age was 30 years (interquartile range [IQR], 23–36 years). Sixty patients were diagnosed with UC, including 32 men (53.3%) and 28 women (46.7%); the median age was 36.5 years (IQR, 25–46.76 years). IBD diagnoses were based on

classic histological, endoscopic, and radiological criteria.²¹ The exclusion criteria were pregnancy, diabetes, immune diseases, other serious diseases, and chronic inflammatory processes.

The control group consisted of 31 healthy volunteers, including 13 men (41.9%) and 18 women (58.1%); the median age was 39 years (IQR, 31–45 years). All patients provided written informed consent to participate in the study. The study protocol was approved by the Jagiellonian University Ethics Committee.

Clinical assessment Detailed histories of IBD were taken from all participants. Data on the following parameters were collected: smoking habit, disease activity, disease duration, location of pathological changes, complications, current medications, and past surgical procedures. The Montreal classification was used to assess lesion location in patients with UC and CD.²² Complications were defined as the presence of abscesses, fistulas, obstructions, or extraintestinal diseases associated with IBD.²³

Disease activity was assessed according to the Crohn Disease Activity Index (CDAI) for patients with CD and the Mayo Score for those with UC.^{24,25} Patients with CD were divided into 2 subgroups based on CDAI scores: nonactive CD (CDAI score <150, $n = 33$ [47.8%]) and active CD (active CD; CDAI score ≥ 150 , $n = 36$ [52.2%]).²⁶ Patients with UC were also divided into 2 subgroups based on Mayo scores: nonactive UC (nonactive UC; Mayo score = 1–3, $n = 31$ [51.7%]) and active UC (Mayo score ≥ 4 , $n = 29$ [48.3%]).

Laboratory analyses Routine laboratory tests and complete blood counts were performed in all participants. Serum biochemical analyses included the examination of C-reactive protein (CRP), albumin, and fibrinogen levels. All tests were performed using routine methodology in clinical practice. Complete blood counts were performed with a Sysmex XE-2100 automated hematological analyzer (Sysmex, Kobe, Japan). CRP and albumin levels were assayed using the Modular P clinical chemistry analyzer (Roche Diagnostics, Mannheim, Germany). Fibrinogen levels were measured with a Behring coagulation system (Dade Behring, Marburg, Germany). TNF- α and interleukin-6 (IL-6) concentrations were determined by an enzyme-linked immunosorbent assay (ELISA) with the ELISA Quantikine Immunoassay Kit (R&D Systems, Minneapolis, Minnesota, United States). The serum levels of IGF-1 and IGFBP-3 were determined by ELISA using the Quantikine Human IGF-1 and IGFBP-3 ELISA kits (R&D Systems).

Statistical analysis Continuous data were presented as means with standard deviations (normally distributed data) or as medians with lower and upper quartiles (skewed distributions). Discrete data were presented as frequencies and percentages. A 1-way analysis of variance was

TABLE 1 Laboratory markers in patients with active and nonactive ulcerative colitis and control group

Parameter	Nonactive UC (n = 31)	Active UC (n = 29)	Control group (n = 31)
Male sex, n (%)	17 (54.8)	15 (51.7)	13 (41.9)
Age, y	29 (25–47.5)	40 (30–46)	39 (31–45)
Mayo score, points	2 (1–3) ^a	7 (6–9)	NA
Disease duration, y	6 (2.5–9.5)	5 (2–9)	NA
CRP, mg/l	1.2 (0.8–1.9) ^a	10 (7.4–42.2) ^b	0.65 (0.45–1.1)
WBC, × 10 ³ /μl	6.1 (5.3–7.3) ^a	8.9 (6.9–11.2) ^b	6.2 (4.9–7.7)
RBC, × 10 ⁶ /μl, mean (SD)	4.8 (0.6)	4.6 (0.5)	4.7 (0.4)
Hemoglobin, g/dl	13.8 (12.8–15) ^a	12.7 (11.7–13.8) ^b	14.3 (13.2–15.6)
Hematocrit, %	43.2 (39.3–44.6)	39.7 (36.8–42.2)	41 (38.6–44.6)
Platelets, × 10 ³ /μl	235 (201–288.5) ^a	316 (238–354) ^b	198 (185–251.5)
Albumin, g/l	45 (42.5–47.5) ^a	41 (35–43) ^b	47 (43.5–48)
Fibrinogen, g/l	2.6 (2.4–3.6) ^a	4.7 (3.6–6.4) ^b	2.7 (2.4–3)
TNF-α, mg/l	1.5 (1.2–2.4)	2.4 (1.4–3.6)	1.3 (0.9–1.6)
IL-6, pg/ml,	1.3 (.9–2.9) ^a	3.3 (1.6–9.9)	1.7 (1–2.9)
IGF-1, ng/ml, mean (SD)	96.2 (24.5) ^a	78.3 (22.7) ^b	94.5 (26.5)
IGFBP-3, ng/ml	2003.6 ^a (1777.8–2238.8)	1678.8 ^b (1411.7–200.2)	2038.3 (1677.1–3060)

Data are presented as median (interquartile range) unless otherwise stated.

a $P < 0.05$ compared with active UC

b $P < 0.05$ compared with the control group

Abbreviations: CRP, C-reactive protein; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor-binding protein 3; IL-6, interleukin 6; NA, not applicable; RBC, red blood cells; TNF-α, tumor necrosis factor α; UC, ulcerative colitis; WBC, white blood cells

employed to compare the mean values among the 3 different populations, providing all assumptions were met; otherwise, the Kruskal–Wallis test (for nonnormally distributed data) or Welch test (in case of heterogeneity) was applied. Additionally, the post hoc Tukey test was performed in cases of significant results. Normality was verified by the Shapiro–Wilk test, and homogeneity of variance was determined by the Levene test. The association between 2 continuous variables was investigated using the Pearson or Spearman rank correlation analysis, and the association between 2 discrete variables was assessed by the χ^2 test or Fisher exact test.

Additional analyses were performed due to statistically significant differences in the mean age between the active CD and nonactive CD groups and healthy controls. Multiple linear regressions were applied to compare the means of selected features between these groups after adjusting for age. The interaction between age and disease activity was included in the models. The Shapiro–Wilk test was used to verify whether the residuals were distributed normally, and the Breusch–Pagan test was applied to investigate heteroscedasticity. Dependent variables were transformed logarithmically in cases of nonnormally distributed residuals or heteroscedasticity. The results were considered significant when P values were less than 0.05. The R software (version 3.3.2, The R Foundation

for Statistical Computing, Vienna, Austria) was used for the calculations.

RESULTS No significant difference in sex was observed among the UC, CD, and control groups ($P = 0.6$). The median age of patients with CD was lower than those of patients with UC ($P = 0.02$) and healthy participants ($P = 0.004$). The mean (SD) body mass index (BMI) was lower in the CD group than in the control group (21.6 [3.5] kg/m² vs 23.7 [3.4] kg/m², respectively; $P = 0.02$). Seven patients (12%) with UC and 18 patients (26%) with CD had a BMI below 18.5 kg/m², but only 1 patient with UC and 5 patients with CD had a BMI below 17 kg/m². There were 2 obese patients, 1 in the CD group and 1 in the UC group. The numbers of smokers were similar in all groups ($P = 0.2$). The extraintestinal complications occurred more frequently in patients with CD ($P = 0.006$). Patients with CD were also more likely to have undergone surgery ($P < 0.001$).

None of the analyzed patients had been biologically treated prior to the study. On enrollment, aminosalicylates were administered to all patients with IBD, immunosuppressants to 10 patients with UC (17%) and 26 patients with CD (38%), and corticosteroids to 17 patients with UC (28%) and 23 patients with CD (33%). The distribution of treatment used was not different in patients with UC and CD ($P = 0.062$).

The clinical characteristics of patients with active UC, nonactive UC, and healthy participants

TABLE 2 Laboratory markers in patients with active and nonactive Crohn disease and control group

Parameter	Nonactive CD (n = 33)	Active CD (n = 36)	Control group (n = 31)
Male sex, n (%)	15 (45.5)	21 (58.3)	13 (41.9)
Age, y	30 (23–36) ^b	31 (23.8–36) ^b	39 (31–45)
CDAI score, points	70.4 (55–101.8) ^a	228 (172.4–287.3)	NA
Disease duration, y	3 (2–6)	4 (2–7.3)	NA
CRP, mg/l	1.5 (0.5–3.6) ^a	24.4 (16.1–62.2) ^b	0.65 (0.45–1.1)
WBC, $\times 10^3/\mu\text{l}$	6.2 (5.6–7.2)	7 (5.4–9.4)	6.2 (4.9–7.7)
RBC, $\times 10^6/\mu\text{l}$	4.8 (4.4–5.2)	4.8 (4.2–5)	4.7 (0.4)
Hemoglobin, g/dl	14.2 (13.1–14.9) ^a	12.1 (10.9–13.2) ^b	14.3 (13.2–15.6)
Hematocrit, %	42.2 (40.1–45.5) ^a	37.9 (35–40.6) ^b	41 (38.6–44.6)
Platelets, $\times 10^3/\mu\text{l}$	277 (215–305) ^{a,b}	324.5 (287.5–404.5) ^b	198 (185–251.5)
Albumin, g/l, mean (SD)	44.1 (3.8) ^a	38 (5.3) ^b	45.8 (2.7)
Fibrinogen, g/l	3.1 (2.6–4.2) ^a	5.2 (4.4–6.9) ^b	2.7 (2.4–3)
TNF- α , mg/l	1.1 (1–1.7) ^a	1.9 (1.4–3) ^b	1.3 (.9–1.6)
IL-6, pg/ml	1.3 (1–6.6) ^a	4.4 (2–6.6) ^b	1.7 (1–2.9)
IGF-1, ng/ml, mean (SD)	110.1 (43.4) ^a	79.2 (24.9)	94.5 (26.5)
IGFBP-3, ng/ml	2001.8 (1863.6–2191.5)	1881.4 (1714.4–2121)	2038.3 (1677.1–3060)

Data are presented as median (interquartile range) unless otherwise stated.

a $P < 0.05$ compared with active CD

b $P < 0.05$ compared with the control group

Abbreviations: CD, Crohn disease; CDAI, Crohn Disease Activity Index; others, see [TABLE 1](#)

are shown in [TABLE 1](#). The medians of the inflammatory markers were higher in the active UC group than in the nonactive UC and control groups. Patients with active UC had a significantly higher median level of IL-6 than patients with nonactive UC. The mean IGF-1 concentration and median IGFBP-3 concentration were lower in the active UC group than in the nonactive UC group and the control group.

Laboratory markers in the active CD, nonactive CD, and control groups are presented in [TABLE 2](#). Patients with active CD demonstrated higher concentrations of inflammatory markers, including TNF- α , compared with patients in the nonactive CD group and controls. The mean IGF-1 level was significantly lower in the active CD group than in the nonactive CD group. No difference in the median IGFBP-3 level was observed among the 3 studied populations.

In the nonactive UC group, only 1 person (3.2%) received corticosteroids. The IGF-1 value for this patient was 80.2 ng/ml, whereas the average IGF-1 level for the remaining 30 participants was 96.7 ng/ml (95% confidence interval [CI], 87.5–105.9). In the active UC group, 16 of 29 patients (55.2%) received corticosteroids. The mean IGF-1 value in this group was 80.2 ng/ml (95% CI, 66.3–94.2) and did not differ significantly from the mean IGF-1 value in the noncorticosteroid group (76 ng/ml; 95% CI, 65–87).

In the nonactive CD group, 10 of 33 patients (30.3%) received corticosteroids. The average

IGF-1 value in this group was 103.7 ng/ml (95% CI, 74.1–133.3) and did not differ significantly from the mean IGF-1 value in the noncorticosteroid group (112.9 ng/ml; 95% CI, 93.5–132.3). In the active CD group, 13 of 36 patients (36.1%) received corticosteroids. The mean IGF-1 value in this group was 82.5 ng/ml (95% CI, 64.3–100.7) and did not differ significantly from the mean IGF-1 value in the noncorticosteroid group, (77.3 ng/ml; 95% CI, 67.8–86.8).

Multiple linear regressions were performed due to significant differences in the mean age between the active CD group, nonactive CD group, and healthy controls, as well as significant correlations between age and such variables as disease duration ($r = 0.3$; $P = 0.01$), IGF-1 ($r = -0.5$; $P < 0.001$), and IGFBP-3 ($r = -0.3$; $P = 0.006$). Logarithmic transformation was applied to these 3 variables because of nonnormally distributed residuals and/or heteroscedasticity. The results showed that the interaction term (age \times group) and term with age only were not significant predictors of the logarithm of disease duration. Also the interaction terms were not significant predictors of the logarithm of IGFBP-3, as opposed to age. It was a significant predictor of the logarithm of IGFBP-3 ($\beta = 0.01$; $P = 0.02$). The IGFBP-3 level in the study groups decreased by 0.99 each year. Notably, the mean disease duration and IGFBP-3 level did not differ significantly between the groups after adjusting for age.

FIGURE 1 Scatterplot of insulin-like growth factor 1 (IGF-1) and age according to Crohn disease activity

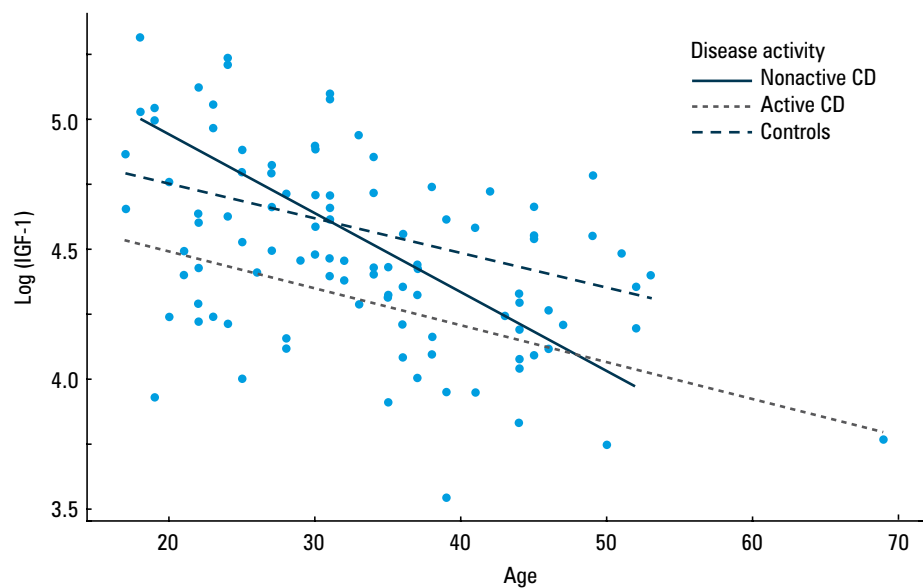


TABLE 3 Coefficients of correlation between insulin-like growth factor 1 and given properties in the populations separately

Parameter	UC (n = 60)	CD (n = 69)	Control group (n = 31)
CRP, mg/l	$r = -0.4$ $P = 0.002$	$r = -0.3$ $P = 0.009$	NS
WBC, $\times 10^3/\mu\text{l}$	NS	NS	NS
RBC, $\times 10^6/\mu\text{l}$	NS	NS	NS
Hemoglobin, g/dl	NS	$r = 0.3$ $P = 0.02$	NS
Hematocrit, %	NS	$r = 0.3$ $P = 0.02$	NS
Platelets, $\times 10^3/\mu\text{l}$	NS	$r = -0.3$ $P = 0.04$	NS
Albumin, g/l	$r = 0.3$ $P = 0.02$	$r = 0.3$ $P = 0.03$	NS
Fibrinogen, g/l	$r = -0.4$ $P = 0.003$	$r = -0.4$ $P = 0.003$	NS
TNF- α , mg/l	NS	NS	NS
IL-6, pg/ml	$r = -0.3$ $P = 0.02$	NS	NS
CDAI / Mayo scores	$r = -0.3$ $P = 0.02$	$r = -0.4$ $P = 0.003$	NA
Disease duration, y	$r = -0.3$ $P = 0.01$	$r = -0.3$ $P = 0.02$	NA
IGFBP-3, ng/ml	$r = 0.4$ $P = 0.002$	$r = 0.5$ $P < 0.001$	$r = 0.38$ $P = 0.035$

Abbreviations: NS, nonsignificant; others, see TABLES 1 and 2

Significant interaction terms were discovered in the case of the IGF-1 marker. The mean values of the logarithm of IGF-1 in the nonactive CD group differed from those in the active CD group by $0.78 - 0.02 \times \text{age}$ ($P = 0.03$) (FIGURE 1). Similar age-related differences were found between the nonactive CD and control groups. The mean

value of the logarithm of IGF-1 in the nonactive CD group differed from that in the control group by $0.54 - 0.02 \times \text{age}$ ($P = 0.03$). No significant interaction was found between the active CD group and the control group ($P = 0.9$). In this situation, lower values of the logarithm of IGF-1 were not significantly related to age. The difference in the mean logarithm of IGF-1 between the active CD and control groups remained stable, regardless of age.

The correlations of IGF-1 and IGFBP-3 with the other parameters in all patient groups are presented in TABLES 3 and 4, respectively.

DISCUSSION This study is the first to demonstrate that plasma IGF-1 levels are lower in patients with active UC and active CD than in patients in remission. Similarly, the mean IGFBP-3 level was lower in patients with UC flares. In addition, this study showed that IGF-1 in patients with IBD was correlated negatively with clinical activity of the disease, disease duration, and inflammatory markers. On the other hand, IGFBP-3 was correlated negatively with inflammatory markers and disease activity in patients with UC.

Eivindson et al²⁷ demonstrated that the serum IGF-1 level is correlated negatively with CRP levels and positively with albumin levels in patients with IBD, whereas IGFBP-3 is correlated positively with the albumin level in patients with IBD and negatively with the UC activity; however, no significant difference in the mean IGF-1 or IGFBP-3 value was shown during disease flares or remissions. The authors concluded that the IGF system of proteins is associated with the activity of the inflammatory state, which was confirmed by our finding of lower IGF-1 concentrations in patients during IBD flares, as well as differences in IGFBP-3 concentrations in those with active UC.

Street et al,²⁸ who analyzed data from 37 patients with CD and UC, observed that the IGF-1

TABLE 4 Coefficients of correlation between insulin-like growth factor binding protein 3 and given properties in the populations separately

	UC (n = 60)	CD (n = 69)	Control group (n = 31)
CRP, mg/l	$r = -0.4$ $P = 0.004$	$r = -0.3$ $P = 0.01$	NS
WBC, $\times 10^3/\mu\text{l}$	$r = -0.3$ $P = 0.05$	NS	NS
RBC, $\times 10^6/\mu\text{l}$	NS	NS	NS
Hemoglobin, g/dl	NS	NS	NS
Hematocrit, %	NS	NS	NS
Platelets, $\times 10^3/\mu\text{l}$	NS	NS	$r = 0.4$ $P = 0.04$
Albumin, g/l	NS	NS	NS
Fibrinogen, g/l	$r = 0.3$ $P = 0.02$	NS	NS
TNF- α , mg/l	NS	NS	NS
IL-6, pg/ml	NS	NS	NS
CDAI / Mayo scores	$r = -0.3$ $P = 0.01$	NS	NA
Disease duration, y	NS	NS	NA

Abbreviations: see TABLES 1, 2, and 3

level was lower in patients with CD compared with healthy participants only during disease flares. In addition, the IGFBP-3 level did not differ between these groups. However, the authors defined a disease flare as a CRP concentration exceeding 1.5 mg/l and erythrocyte sedimentation rate exceeding 20 mm/h, which may have resulted in the failure to appropriately identify some patients with disease flares. On the other hand, Katsanos et al²⁹ analyzed data from 22 patients with newly diagnosed IBD (not divided into CD and UC subgroups) and demonstrated a decrease in IGF-1 and IGFBP-3 levels in affected participants compared with healthy individuals who were matched for age, sex, and BMI. The results of our study, which was performed with more participants and included the analyses of the CD and UC subgroups during disease flares and remission, confirmed abnormalities in the IGF axis functioning during active inflammation in patients with IBD.

Interesting results were obtained in studies carried out with IGFBP-3 knockout mice, in which UC was induced by administering dextran sodium sulfate. IGFBP-3 knockout mice demonstrated a less active inflammatory state and lower levels of IL-6, TNF- α , and IL-1 β , as well as increased proliferation of intestinal endothelial cells leading to repair of the endothelial barrier, which might confirm the role of the IGF axis in the development of the inflammatory state in patients with IBD.³⁰ In turn, an experimental study performed by Harris et al³¹ in mice with colitis induced by dextran sodium sulfate showed a decrease in the level of plasma IGF-1; these results are concordant with our observations in adult patients with IBD.

Our study also demonstrated a negative correlation between IGF-1 and IBD duration in the CD and UC groups. Similar observations were reported by Baker et al¹⁸ for patients with rheumatoid arthritis. This phenomenon may be related to increased catabolism due to increased disease duration, which may be responsible for disturbances in the GH/IGF-1 axis.²⁷ Katsanos et al²⁹ suggested that the decreases in IGF-1 and IGFBP-3 levels in patients with active IBD could be associated with acquired GH resistance, which can be caused by inflammatory cytokines.

Numerous patients with IBD also suffer from osteopenia or osteoporosis, and they show lower calcium and phosphate levels as compared with healthy people.³² A decrease in the concentration of IGF-1, hormone responsible for normal growth of bones and muscles, as well as a decrease in the level of IGFBP-3 are among the factors contributing to muscle weakness and osteoporosis in patients with IBD.^{28,31,33,34} These abnormalities intensify with prolonged disease duration. Van Langenberg et al³³ found that a decrease in the IGF-1 level was associated with muscle weakening in patients with CD; however, disease duration was not considered and the analysis did not include patients with UC. Among the studies of osteoporosis in patients with IBD, only Koutroubakis et al³⁴ analyzed correlations between the IGF-1 and IGFBP-3 levels and the intensification of osteoporosis in patients with IBD. They noted a weak positive correlation between IGFBP-3 and bone mineral density of the femoral neck. The authors concluded that low concentrations of IGF-1 and IGFBP-3 might decrease bone mineral density.

An important factor that might contribute to the development of osteoporosis in patients with IBD is the use of glucocorticoids. Glucocorticoids affect differentiation and function of osteoblasts, metabolism, and function of osteocytes; moreover, they are involved in the regulation of GH secretion.³⁵ Glucocorticoid excess may suppress the peripheral expression of GH-receptors impairing the IGF-1 synthesis;³⁵ however, high therapeutic doses have been shown to increase IGF-1 levels, while the bioavailability of this hormone is reduced.⁵ In our study, we did not observe significant differences in IGF-1 levels between patients who received glucocorticoids and those who did not.

IGF-1 acts as a vasodilator. Individuals with GH deficits and low IGF-1 levels manifest endothelial dysfunction and abnormalities of vasodilation depending on nitric oxide produced by endothelial cells.³⁶ Earlier in vivo studies demonstrated that IGF-1 stimulation induces endothelial nitric oxide synthase.³⁷ Nitric oxide is a key factor in the maintenance of normal vascular homeostasis.¹ Its production is disturbed by asymmetric dimethylarginine (ADMA), which is an endogenous inhibitor of endothelial nitric oxide synthase.³⁸ ADMA has been recognized as a marker of endothelial dysfunction, and ADMA

levels increase in patients with IBD.^{39,40} Thus, an increase in the ADMA concentration and a decrease in the IGF-1 concentration disturb vascular endothelial function and depress nitric oxide synthesis, contributing to the escalation of the inflammatory state and oxidative stress.

IGF-1 is also involved in intestinal extracellular matrix remodeling and collagen regulation, which consistently promote fibrosis, depending on inflammation intensity, in patients with IBD.⁴¹ On the other hand, IGF-1 activates growth and regeneration of intestinal epithelium and, along with transforming growth factor β , is involved in wound-healing mechanisms.^{42,43} IGF-1 and IGFBP-3 are present in significant concentrations in wound fluid.⁴¹ Biochemical studies have shown that IGFBP-3 and IGF-1 complexes bind with high affinity to fibrinogen and fibrin, which might be an important mechanism by which IGF-1 levels are maintained at the wound site.⁴⁴ We hypothesized that the IGF axis participates in the pathogenesis of IBD by acting on the endothelium and the coagulation system.

Some reports have demonstrated a positive correlation between the IGF-1 concentration and fibrinogen.^{45,46} On the other hand, Colao et al⁴⁷ showed that IGF-1 levels in patients with GH deficiency are inversely correlated with fibrinogen levels. Similarly, Fornari et al⁴⁸ demonstrated negative correlations of IGF-1 with concentrations of fibrinogen and other inflammatory markers in obese patients. In our study, we found a negative correlation between IGF-1 and fibrinogen levels in patients with IBD, which was likely associated with an increase in fibrinogen as an acute-phase protein during the inflammatory process.

We also detected positive correlations between IGF-1 and hemoglobin and hematocrit levels in patients with CD. Patients with anemia have significantly lower IGF-1 concentrations.⁴⁹ The postulated pathomechanism includes IGF-1-dependent impaired stimulation of the erythropoiesis pathway, as well as disturbances in erythropoietin secretion resulting from increased concentrations of proinflammatory cytokines.⁴⁸

The use of IGF-1 gene therapy as well as recombinant IGF-1 may be useful for the stimulation of growth in pediatric patients and may be helpful for the reduction of chronic inflammation in patients with IBD.⁵⁰ However, the conclusion should be drawn carefully, as such therapy may also aggravate fibrosis in patients with CD and facilitate transformation to malignancy. Moreover, it is associated with numerous side effects.⁵⁰ Data on the IGF axis in IBD remain scarce, and further research is necessary to verify the importance of IGF-1 and IGFBP-3 in the pathogenesis and treatment of IBD.

Our study has several limitations, including the lack of assessment of insulin levels, nutritional state, and physical activity and analysis of osteoporosis in study participants.

In conclusion, our results show that the IGF system is disrupted in patients with IBD. The systemic levels of the IGF axis components are related to disease activity and duration. Our results support the role of the IGF axis in the pathogenesis of IBD.

Contribution statement DO, MK-S, and DC conceived the idea for the study. DO, MK-S, and DC contributed to the design of the research. DO, MK-S, DC, and KS were involved in data collection. MK-S, DC, KS, and RD-R analyzed and interpreted the data. All authors drafted the manuscript, as well as edited and approved the final version of the manuscript.

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